

# Cardiorespiratory Fitness and Metabolic Syndrome in Older Men and Women

## The Dose Responses to Exercise Training (DR's EXTRA) study

MAIJA HASSINEN, PHD<sup>1</sup>  
TIMO A. LAKKA, MD<sup>1,2</sup>  
LEENA HAKOLA, MSC<sup>1</sup>  
KAI SAVONEN, MD<sup>1,3</sup>  
PIRJO KOMULAINEN, PHD<sup>1</sup>

HANNU LITMANEN, MD<sup>1</sup>  
VESA KIVINIEMI, PHD<sup>4</sup>  
REIJA KOUKI, MSC<sup>1</sup>  
HARRI HEIKKILÄ, MSC<sup>1</sup>  
RAINER RAURAMAA, MD<sup>1,3</sup>

**OBJECTIVE** — We studied the association of maximum oxygen uptake ( $Vo_{2max}$ ) with the development and resolution of metabolic syndrome (MetS) for 2 years in older individuals.

**RESEARCH DESIGN AND METHODS** — Subjects were a population sample of 1,226 men and women aged 57–78 years. We assessed  $Vo_{2max}$  directly by respiratory gas analysis during maximum exercise testing and used dichotomous and continuous variables for MetS.

**RESULTS** — One SD increase in baseline  $Vo_{2max}$  associated with 44% (95% CI 24–58) decreased risk of developing MetS. Individuals in the highest third of baseline  $Vo_{2max}$  were 68% (37–84) less likely to develop MetS than those in the lowest third. One SD increase in  $Vo_{2max}$  increased the likelihood to resolve MetS 1.8 (1.2–2.8) times. Individuals in the highest  $Vo_{2max}$  third were 3.9 (1.5–9.9) times more likely to resolve MetS than those in the lowest third.

**CONCLUSIONS** — Higher levels of cardiorespiratory fitness protect against MetS and may resolve it in older individuals.

*Diabetes Care* 33:1655–1657, 2010

Cross-sectional population studies have shown an inverse association between cardiorespiratory fitness (CRF) and the metabolic syndrome (MetS) in middle-aged and older men and women (1,2). There are few prospective population studies on the association between CRF and the development of MetS (3–6) and no such studies on the resolution of MetS. None of these studies have been conducted in older men and women. Evidence of the association between changes in CRF and metabolic risk rely on relatively small prospective studies among middle-aged or high-risk individuals (6,7). We therefore studied the association of maximum oxygen uptake ( $Vo_{2max}$ ) with the development and reso-

lution of MetS and changes in  $Vo_{2max}$  and metabolic risk in a population sample of older men and women.

### RESEARCH DESIGN AND METHODS

We used baseline and 2-year follow-up data of an ongoing randomized controlled trial, the Dose Responses to Exercise Training (DR's EXTRA) study, which includes five intervention groups and one control group (2). After excluding individuals with diabetes or incomplete data, analyses consisted of 589 men and 637 women aged 57–78 years.

CRF was assessed by a respiratory gas analysis during a maximum symptom-limited exercise test on a cycle ergometer

(2). Physical activity was assessed by a questionnaire, and dietary intake was assessed by a 4-day food record including 3 weekdays and 1 weekend day. MetS was defined by the National Cholesterol Education Program (NCEP) criteria (8), and a metabolic risk score ( $z$ -MetS) was constructed (5,7). Other assessments have previously been explained (2).

The associations of baseline  $Vo_{2max}$  with the development and resolution of MetS during 2 years were analyzed using logistic regression analysis ( $n = 1,137$ ) and the 2-year associations of  $Vo_{2max}$  with  $z$ -MetS and features of MetS by linear mixed models ( $n = 1,226$ ). Statistical analyses were performed using SPSS.

**RESULTS** — At baseline, 22% of men and women had MetS. Of 427 men and 466 women without MetS at baseline, 44 and 49, respectively, developed it during 2 years. Of 117 men and 127 women with MetS at baseline, 47 and 38, respectively, resolved it during 2 years.

Among individuals without MetS at baseline, 1-SD higher baseline  $Vo_{2max}$  (men 6.1, women 4.8  $ml \cdot kg^{-1} \cdot min^{-1}$ ) was associated with a 44% (95% CI 24–58) decreased risk of developing MetS during 2 years in all individuals; a 56% (27–73) decreased risk in men; and a 35% (4–56) decreased risk in women adjusted for age, smoking, alcohol consumption, cardiovascular diseases, NCEP metabolic risk sum, and study groups at baseline. Individuals in the highest sex-specific third of baseline  $Vo_{2max}$  were 68% less likely to develop MetS than those in the lowest third (Table 1). Further adjustments for physical activity and dietary intakes (saturated, monounsaturated, and polyunsaturated fatty acids, fiber, and carbohydrates) at baseline and study groups did not affect the association, but adjustment for body weight at baseline and changes in body weight during 2 years diminished it.

Among individuals with MetS at baseline, 1-SD higher  $Vo_{2max}$  was associated with a 1.8 (1.21–2.82) times higher likelihood to resolve MetS during 2 years in all individuals; a 2.1 (1.12–3.96) times

From the <sup>1</sup>Kuopio Research Institute of Exercise Medicine, Kuopio, Finland; the <sup>2</sup>Institute of Biomedicine/Physiology, University of Eastern Finland, Kuopio Campus, Kuopio, Finland; the <sup>3</sup>Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland; and the <sup>4</sup>Information Technology Centre, University of Eastern Finland, Kuopio Campus, Kuopio, Finland.

Corresponding author: Rainer Rauramaa, rainer.rauramaa@uef.fi.

Received 21 January 2010 and accepted 31 March 2010. Published ahead of print at <http://care.diabetesjournals.org> on 22 April 2010. DOI: 10.2337/dc10-0124. Clinical trial registry no. ISRCTN 45977199, ISRCTN.org.

© 2010 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

**Table 1—Odds ratios (95% CI) for the development and resolution of the metabolic syndrome during 2 years in the sex-specific thirds of maximum oxygen uptake at baseline**

Thirds of maximum oxygen uptake*	Odds for incident metabolic syndrome		
	Model 1	Model 2	Model 3
<i>n</i>		893	
Low (reference)	1	1	1
Middle	0.76 (0.43–1.33)	0.75 (0.42–1.34)	0.96 (0.51–1.78)
High	0.32 (0.16–0.64)	0.32 (0.16–0.63)	0.47 (0.22–1.01)
<i>P</i> for trend	0.001	0.001	0.055
	Odds for resolved metabolic syndrome		
<i>n</i>		244	
Low (reference)	1	1	1
Middle	1.23 (0.64–2.38)	1.37 (0.69–2.74)	1.40 (0.66–2.96)
High	3.89 (1.54–9.85)	4.66 (1.78–12.19)	5.54 (1.93–15.94)
<i>P</i> for trend	0.010	0.004	0.004

Data are from logistic regression analysis. Model 1: adjusted for baseline age, smoking, alcohol consumption, cardiovascular disease, and NCEP metabolic risk sum. Model 2: adjusted for variables in model 1, the study groups, physical activity, and intake of saturated, monounsaturated, and polyunsaturated fatty acids, fiber, and carbohydrates. Model 3: adjusted for variables in models 1 and 2, body weight at baseline, and change in body weight during 2 years. \*In men: low <23.3, middle 23.3–29.1, and high >29.1 ml · kg<sup>-1</sup> · min<sup>-1</sup>. In women: low <18.4, middle 18.4–22.8, and high >22.8 ml · kg<sup>-1</sup> · min<sup>-1</sup>.

higher likelihood in men; and a 1.9 (0.98–3.70) times higher likelihood in women after baseline adjustments. Individuals in the highest third of Vo<sub>2max</sub> were 3.9 times more likely to resolve MetS than those in the lowest third (Table 1). Further adjustments slightly strengthened the association.

One ml · kg<sup>-1</sup> · min<sup>-1</sup> increase in Vo<sub>2max</sub> was associated with a 0.19 unit (95% CI –0.17 to –0.21) reduction in z-MetS adjusted for age, sex, and study groups. Further adjustment for smoking, alcohol consumption, use of lipid-lowering and antihypertensive medication, cardiovascular diseases, physical activity, and dietary intakes during 2 years did not materially change the association. One ml · kg<sup>-1</sup> · min<sup>-1</sup> increase in Vo<sub>2max</sub> was also associated with a reduction in waist circumference ( $\beta = -0.47$ ,  $P < 0.001$ ), fasting glucose ( $\beta = -0.02$ ,  $P < 0.001$ ), triglycerides ( $\beta = -0.03$ ,  $P < 0.001$ ), systolic blood pressure ( $\beta = -0.29$ ,  $P = 0.001$ ), diastolic blood pressure ( $\beta = -0.20$ ,  $P < 0.001$ ), and an increase in HDL cholesterol ( $\beta = 0.02$ ,  $P < 0.001$ ) after adjustments for age, sex, and study groups.

**CONCLUSIONS**— The present study suggests that higher levels of CRF protect against the development of MetS and may also resolve it over 2 years among older men and women. The most fit individuals were about 70% less likely to develop

MetS and four times more likely to resolve it than the least fit individuals. Increased CRF improved the components of MetS and the overall metabolic risk profile during 2 years.

We have previously reported that older men and women in the lowest third of Vo<sub>2max</sub> had 10 times higher risk of MetS than the most fit individuals (2) and that higher levels of cardiorespiratory fitness protected against the development of MetS during 4 years in middle-aged men (3). Also, CRF in young adulthood was inversely associated with the risk of developing MetS, type 2 diabetes, and hypertension in middle-age (4). In contrast, no independent association between CRF and the development of MetS was found in middle-aged individuals after controlling for physical activity (5,6). In the present study, the association between CRF and MetS remained after adjustment for physical activity and dietary intakes.

Physical activity is the principal determinant of CRF, although genetic variation, age, and body composition also contribute (9). Middle-aged men who have higher levels of CRF and who are able to maintain good CRF are physically more active and have higher lean body mass and lower body fat mass than those who have worse CRF. These individuals have improved carbohydrate and fat me-

tabolism that can protect against or even resolve MetS (10).

The study population included a large number of older men and women recruited from the national population register. We assessed Vo<sub>2max</sub> directly by respiratory gas analysis during a maximum exercise test, which is the most accurate measure of CRF. While most other studies have only focused on the incidence of MetS, we studied the incidence and resolution of MetS. We also used a continuous metabolic risk score as an outcome variable to increase statistical power to detect true associations.

In conclusion, the present study emphasizes CRF as a predictor of cardio-metabolic health in older individuals with and without MetS.

**Acknowledgments**— This study was supported by grants from the Ministry of Education in Finland, Academy of Finland, European Commission FP6 Integrated Project EXGENESIS (LSHM-CT-2004-00527), the City of Kuopio, Finnish Diabetes Association, Finnish Heart Association, Kuopio University Hospital, and Päivikki and Sakari Sohlberg Foundation.

No potential conflicts of interest relevant to this article were reported.

M.H., T.A.L., and R.R. contributed to the study conception and design. M.H., T.A.L., V.K., and R.R. researched the data. M.H. wrote the manuscript. M.H., T.A.L., K.S., and P.K. reviewed and edited the manuscript. T.A.L., L.H., K.S., P.K., H.L., R.K., H.H., and R.R. contributed to the discussion. M.H., L.H., K.S., P.K., H.L., R.K., and H.H. contributed to the data collection. V.K. contributed as a statistical consultant. R.R. is a guarantor of the study.

## References

- Lakka TA, Laaksonen DE, Lakka HM, Männikkö N, Niskanen LK, Rauramaa R, Salonen JT. Sedentary lifestyle, poor cardiorespiratory fitness, and the metabolic syndrome. *Med Sci Sports Exerc* 2003;35:1279–1286
- Hassinen M, Lakka TA, Savonen K, Litmanen H, Kiviahho L, Laaksonen DE, Komulainen P, Rauramaa R. Cardiorespiratory fitness as a feature of the metabolic syndrome in older men and women: the Dose-Responses to Exercise Training study (DR's EXTRA). *Diabetes Care* 2008;31:1242–1247
- Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R, Lakka TA. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. *Diabetes Care* 2002;25:1612–1618

4. Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs DR Jr, Liu K. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA* 2003;290:3092–3100
5. Ekelund U, Brage S, Franks PW, Hennings S, Emms S, Wareham NJ. Physical activity energy expenditure predicts progression toward the metabolic syndrome independently of aerobic fitness in middle-aged healthy Caucasians: the Medical Research Council Ely Study. *Diabetes Care* 2005;28:1195–1200
6. Ekelund U, Franks PW, Sharp S, Brage S, Wareham NJ. Increase in physical activity energy expenditure is associated with reduced metabolic risk independent of change in fatness and fitness. *Diabetes Care* 2007;30:2101–2106
7. Simmons RK, Griffin SJ, Steele R, Wareham NJ, Ekelund U, ProActive Research Team. Increasing overall physical activity and aerobic fitness is associated with improvements in metabolic risk: cohort analysis of the ProActive trial. *Diabetologia*. 2008;51:787–794
8. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497
9. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc*. 2001;33: S446–S451
10. Laukkanen JA, Laaksonen D, Lakka TA, Savonen K, Rauramaa R, Mäkikallio T, Kurl S. Determinants of cardiorespiratory fitness in men aged 42 to 60 years with and without cardiovascular disease. *Am J Cardiol* 2009;103:1598–1604